JOURNAL OF APPLIED PHYSIOLOGY
Vol. 28, No. 5, May 1970. *Printed in U.S.A.*

Effect of inspired P_{CO_2} up to 30 mm Hg on response of normal man to exercise

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MENN, STUART J., RICHARD D. SINCLAIR, AND B. E. WELCH. *Effect of inspired P_{CO_2} up to 30 mm Hg on response of normal man to exercise.* J. Appl. Physiol. 28(5): 663–671. 1970.—Trained volunteers performed steady-state moderate exercise (½ maximum $\dot{V}_{O_2}$) and heavy exercise (⅔ maximum $\dot{V}_{O_2}$) in 0, 8, 15, 21, and 30 mm Hg $P_{I_{CO_2}}$ for 30 min on a bicycle ergometer. At CO_2 levels of 8 and 15 mm Hg, no difficulty was encountered by the subjects. The higher levels of hypercapnia caused some respiratory symptoms of "air hunger" (dyspnea) and intercostal muscle pain, but were of mild enough degree to permit all subjects to complete the exercise. Incremental exercise up to work loads producing maximum $\dot{V}_{O_2}$ were also performed. The tolerance to maximum exercise in 21 mm Hg $P_{I_{CO_2}}$ resembled that at ⅔ work load in 30 mm Hg $P_{I_{CO_2}}$. $\dot{V}_E$ during maximum exercise did not vary with the level of inspired CO_2, whereas at submaximal work loads, $\dot{V}_E$ increased as $P_{I_{CO_2}}$ increased. At ⅔ and maximum work loads, $\dot{V}_{CO_2}$ during exercise fell progressively with increasing $P_{I_{CO_2}}$. The ineffective CO_2 removal was accompanied by a decreased alveolar-inspired CO_2 gradient with increasing $P_{I_{CO_2}}$. Inadequate elimination of CO_2 caused respiratory acidosis to be superimposed on the metabolic acidosis normally present during exercise.

hypercapnia; carbon dioxide; respiration; CO_2 tolerance; work/acid-base balance

SPACE AND UNDERSEA EXPLORATION have placed man in sealed environmental situations which require highly efficient gaseous control systems. With the ever-present possibility of malfunction of the system for CO_2 removal, it is imperative to know the extent of man's tolerance and adaptability to increased partial pressures of this gas. Considerable effort has been directed to the study of physiological adjustments of resting man to acute and chronic exposure to increased CO_2 levels (5, 14, 15, 25, 26, 32, 33) and a concept of maximum limits is emerging. However, little is known about interaction of the combined stressors of exercise and hypercapnia. Previous studies of these combined stressors have focused primarily upon ventilation effects (2, 8, 13, 17). Quantitative measurements of gas exchange in the lungs and resulting effects on arterial acid-base balance are not available.

The following experiment was designed to obtain such quantitative data during steady-state and exhaustive exercise in 0, 8, 15, 21, and 30 mm Hg inspired carbon dioxide ($P_{I_{CO_2}}$); $P_{I_{CO_2}} = (P_B - 47)F_{I_{CO_2}}$.

METHODS

Eight US Air Force airmen between 18 and 21 years of age and in excellent physical condition served as volunteers for the experiment. A 3.6 x 3.6 x 2.4 m environmental room equipped with a control system for inspired O_2 ($P_{I_{O_2}}$), $P_{I_{CO_2}}$, and temperature was used. Oxygen and carbon dioxide were continuously monitored with a Beckman model F-3 paramagnetic analyzer and a Beckman LB-1 infrared analyzer, respectively. Both analyzers were calibrated with gases which had been cross-checked for accuracy by Scholander and gas chromatographic techniques. Barometric pressure was monitored by a Wallace and Tiernan absolute pressure gauge, and water vapor was measured by a Cambridge dew point hygrometer. A window air conditioner was used for temperature control.

The desired atmosphere composition was established early each morning and maintained throughout the day or changed to a second CO_2 level following the morning experiments. Approximately 1 hr was required for the stabilization of a new atmosphere. Subjects and investigators entered the environmental room through a 1.0 x 1.5 x 2.4 m transfer lock which prevented disturbance of the internal environments.

In Table 1, the data show the mean resting (time 0) and exercise (time 30 min) O_2 and CO_2 inspired partial pressures for all phases of the study. There was a significant difference between rest and exercise in the chamber O_2 and CO_2 atmosphere only for the 0 mm Hg $P_{I_{CO_2}}$ studies. Comparison of the atmosphere for the various exercise levels revealed no significant differences. The $P_{I_{O_2}}$ was reduced at the higher CO_2 levels in an attempt to prevent the increase in alveolar O_2 tension caused by hypercapnic hyperventilation. Room temperature was held at 68–72 F, and the relative humidity ranged between 65 and 85%.

Experimental Profile

On completion of preliminary medical evaluation studies, the subjects began a 14-day exercise training program using a Collins bicycle ergometer. Following this conditioning period, each subject performed maximum exertion tests on the ergometer which consisted of stepwise increases in work load of 10 w every 3 min, starting at 120 w while maintaining a constant pedal speed of 60 rpm. Respiratory rate and expired air collection were taken at various work loads to

TABLE 1. *Atmospheric conditions*

	Carbon Dioxide Levels, mm Hg				
	0	8	15	21	30
P_{IO_2}, mm Hg*					
Rest	142	145	144	137	133
Exercise	139	145	143	136	133
P	<.001	NS	NS	NS	NS
P_{ICO_2}, mm Hg†					
Rest	.89	8.2	15.1	20.9	30.2
Exercise	3.5	8.3	15.0	20.9	30.0
P	<.001	NS	NS	NS	NS

* O_2 tensions were significantly different only at the 0 mm Hg P_{ICO_2} level between the rest and exercise states. † CO_2 tensions were only significantly different at the 0 mm Hg P_{ICO_2} level between rest and exercise.

determine the maximum oxygen uptake ($\dot{V}O_2$). Watt load/$\dot{V}O_2$ curves were then constructed for each subject. To insure the attainment of maximum $\dot{V}O_2$, each man performed two or three tests and the highest $\dot{V}O_2$ obtained was used. Once the curves were established, work loads in watts which would yield ½ and ⅔ of their maximum $\dot{V}O_2$ were selected for each man. The steady-state exercise experiments in CO_2 were then performed at these work loads. The mean work load for all eight subjects for the ½ and ⅔ levels[1] averaged 130 w (≈800 kg-m/min) and 180 w (≈1,100 kg-m/min), respectively. The ½ work level was associated with a mean heart rate of 138 beats/min while the ⅔ levels produced a heart rate of 168 beats/min.

Steady-State Exercise

The ½ maximum $\dot{V}O_2$ runs were conducted in 0, 8, 15, and 21 mm Hg P_{ICO_2}, while the ⅔ maximum $\dot{V}O_2$ tests were carried out in the same atmospheres plus 30 mm Hg P_{ICO_2}. Six and seven subjects were studied at the ½ and ⅔ work levels, respectively. The breathing system consisted of a Collins triple J low-resistance valve (<2 cm H_2O at 200 liters/min), nose clip, wide-bore tubing (1.5 inch) and a dual-bag collection system. Both bags were flushed with the subjects' expired air for 30 sec prior to the 3-min collection. One hundred-milliliter glass syringes lubricated with lithium chloride were used to collect duplicate air samples from each Douglas bag. These samples were measured for expired O_2 and CO_2 content using Beckman E-2 and LB-1 gas analyzers, respectively, and O_2 measurements were corrected for water vapor. Air volumes were measured with a 120-liter Tissot spirometer. Respiratory rate was measured by a thermistor placed in the expiratory side of the breathing apparatus with readout on a Beckman oscillograph. Rectal temperature was measured with a United Systems Corp. digital thermometer.

Approximately 10 min after the subject entered the chamber, a blood sample was obtained by a percutaneous brachial arterial puncture with a 19-gauge needle. The sample was collected in a 10-ml glass syringe with a heparin-filled dead space. Five minutes later resting cardiopulmonary measurements were recorded. The exercise program was started immediately following these procedures and the work load was increased to the predetermined level within the first 45 sec. The subject exercised at this work load for the next 30 min.

Respiratory and cardiac rates, blood pressure, and body temperature were recorded every 5 min during exercise, and expired air collections were made during the 5th- to 8th- and 27th- to 30th-min periods. A second arterial sample was obtained in the 26th and 27th min of exercise. Blood gas data were obtained for the ⅔ maximum $\dot{V}O_2$ experiments only.

Arterial oxygen tension (Pa_{O_2}) and carbon dioxide tension (Pa_{CO_2}) were measured at 35.4 C using Instrumentation Laboratories ultramicroelectrodes (model no. 113), and pH was measured at 37 C with the Radiometer AME-1.

[1] The terms 1/2 and 2/3 work levels or states used throughout this text refer to that exercise in which 1/2 and 2/3 of maximum $\dot{V}O_2$ was obtained on the preexperimental maximum exertion test.

TABLE 2. *Mean rest-exercise rectal temperature changes for all experiments, °C*

P_{ICO_2}, mm Hg		1/2 Max $\dot{V}O_2$			2/3 Max $\dot{V}O_2$			Max $\dot{V}O_2$		
		Rest	Exer	ΔT	Rest	Exer	ΔT	Rest	Exer	ΔT
0	No.	6	6	6	7	7	7	7	7	7
	$\bar{X}$	37.1	37.7	0.6	37.0	37.9	0.9	37.3	37.8	0.5
	SD	±0.1	±0.3	±0.2	±0.2	±0.3	±0.3	±0.2	±0.1	±0.2
8	No.	5	5	5	7	7	7	7	7	7
	$\bar{X}$	37.0	37.6	0.6	37.0	37.9	0.9	37.2	37.7	0.5
	SD	±0.4	±0.4	±0.2	±0.1	±0.2	±0.2	±0.4	±0.3	±0.1
15	No.	6	6	6	7	7	7			
	$\bar{X}$	37.0	37.6	0.6	37.2	37.9	0.7			
	SD	±0.4	±0.5	±0.4	±0.3	±0.4	±0.3			
21	No.	6	6	6	7	7	7	7	7	7
	$\bar{X}$	36.9	37.5	0.6	37.0	37.8	0.8	37.2	37.7	0.5
	SD	±0.3	±0.3	±0.2	±0.2	±0.3	±0.2	±0.2	±0.3	±0.1
30	No.				7	7	7			
	$\bar{X}$				37.0	37.9	0.8			
	SD				±0.3	±0.4	±0.2			

Blood gas and pH results were corrected to the subject's rectal temperature recorded at the time of arterial blood sampling, and all cited measurements refer to the temperature-corrected values. Table 2 lists the mean resting and end-exercise rectal temperatures for all experiments.

Maximum Exercise Tests

The eight subjects also participated in maximum exertion tests in 0, 8, and 21 mm Hg $P_{I_{CO_2}}$ to determine the effect of hypercapnia on maximum work performance.[2] The profile of these maximum runs involved starting at 50 w, while maintaining a steady pedal speed of 60 rpm, and then increasing the work load by 15 w each minute until exhaustion occurred. Heart rate, respiratory rate, $\dot{V}_E$, $\dot{V}_{CO_2}$, and $\dot{V}_{O_2}$ were obtained during these studies. $\dot{V}_E$ was measured over a 15-sec period after 15 sec of adjustment to each increase in watt load. Collections occurred at rest, 95 w, 125 w, 155 w, and at work loads near maximum $\dot{V}_{O_2}$.

RESULTS

General Observations

The subjects completed all 30-min steady-state and maximum exercise runs at all CO_2 level-work load combinations tested. No difficulty was noticed by the subjects exercising at any work level below 21 mm Hg $P_{I_{CO_2}}$. However, at the 21 mm Hg level and above, there were noticeable respiratory symptoms during exercise at ⅔ maximum and maximum $\dot{V}_{O_2}$, and the subjects were well aware of their increased ventilation. Intercostal muscle pain occurred in two of eight subjects during the maximum exercise run in 21 mm Hg $P_{I_{CO_2}}$. Three other subjects experienced dyspnea during the maximum exertion studies. The subjects stated that the chest pain and dyspnea were the subjective factors terminating exercise rather than muscle fatigue noted at the lower $P_{I_{CO_2}}$ tensions.

At 30 mm Hg $P_{I_{CO_2}}$, six of the seven subjects experienced mild to moderate frontal headaches. These varied considerably in onset and duration and occurred usually in the final minutes of the exercise run and disappeared within 1 hr after exposure.

The appearance of ectopic foci on the precordial ECG was seen in four of eight subjects on nine different occasions. In all cases but one (a premature atrial contraction), these foci originated from below the A-V node. These premature ventricular contractions (PVC's) varied in frequency from 3/min to a trigeminy rhythm alternating with two sinus beats. The incidence of occurrence of PVC's was not related to the level of exercise or the inspired CO_2 environments. In no case did the subjects complain of cardiovascular symptoms.

Steady-State Studies

Ventilation. For any given inspired CO_2 tension, the $\dot{V}_E$ was greater for the ⅔ exercise level than for the ½ level. The results in Table 3 show that at rest, the ½, or the ⅔ state, $\dot{V}_E$ significantly increased with $P_{I_{CO_2}}$ elevation. The rise in $\dot{V}_E$ with different exercise loads was due to an increase in both respiratory rate and tidal volume (V_T), while the rise related to $P_{I_{CO_2}}$ reflects chiefly V_T changes. $\dot{V}_E$ did not significantly change between the 10th and the 30th min in seven of the nine exercise conditions, but did increase slightly during the ⅔ exercise in 8 and 30 mm Hg $P_{I_{CO_2}}$.

$\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, *R.* At the ½ and ⅔ exercise levels, the $\dot{V}_{O_2}$ did not vary significantly with the CO_2 atmospheres (Table 4). Respiratory exchange of CO_2 ($\dot{V}_{CO_2}$) did decrease significantly from 2.43 liters/min (STPD) to 1.84 liters/min as $P_{I_{CO_2}}$ increased from 0 to 30 mm Hg at the ⅔ exercise level. Paralleling the $\dot{V}_{CO_2}$ results, the respiratory exchange ratio fell from .95 to .72 at the ⅔ exercise level. In seven of the nine conditions, a steady state was reached for $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$.

Pulse rate and rectal temperature. Resting and exercise pulse rates at both the ½ and ⅔ work levels did not change with $P_{I_{CO_2}}$. The mean pulse rates were 70.4 ± 3.6 (rest), 139.3 ± 2.9 (½ level), and 166.0 ± 2.0 (⅔ level). Rectal temperature also showed no variation with the different levels of hypercapnia, but did increase an average of 0.3 C between ½ and ⅔ levels of exercise (Table 2).

Acid-base changes. Results of blood gas data are shown in Table 5. The delta values refer to changes between the exercise and rest measurements at each $P_{I_{CO_2}}$ level. Arterial P_{CO_2} increased during exercise from the resting value in the 15, 21, and 30 mm Hg $P_{I_{CO_2}}$ environment. Analysis of variance showed that the difference between exercising and resting Pa_{CO_2} increased significantly with elevation of $P_{I_{CO_2}}$. The ΔpH increased linearly with increasing $P_{I_{CO_2}}$. This occurred because the exercise arterial pH dropped to a greater extent than the resting pH levels with increasing $P_{I_{CO_2}}$. Calculated bicarbonate declined during exercise in all $P_{I_{CO_2}}$ atmospheres but this fall did not follow a linear trend. While resting Pa_{O_2} increased progressively, exercise Pa_{O_2} did not show a linear trend with $P_{I_{CO_2}}$. No arterial desaturation ($Sa_{O_2} < 95\%$) occurred at any $P_{I_{CO_2}}$ level in rest or exercise.

Maximum Exercise Runs

Only $\dot{V}_{CO_2}$ and R changed significantly during maximum exercise in the $P_{I_{CO_2}}$ levels employed (Table 6). These two parameters decreased as the level of $P_{I_{CO_2}}$ increased. $\dot{V}_E$ during maximum $\dot{V}_{O_2}$ did not change with increasing $P_{I_{CO_2}}$. This was in marked contrast to that $\dot{V}_E$ at 155 w ($\approx$½ max $\dot{V}_{O_2}$) which was 19.7 liters higher in 21 mm Hg $P_{I_{CO_2}}$ than in air (see Table 7).

DISCUSSION

General Observations

Headaches have occurred in acute and chronic hypercapnia studies (5, 7, 26, 27, 33) with varying frequency, dependent on the level of $P_{I_{CO_2}}$. Glatte et al. (14) reported occurrence in four of seven subjects exposed to 21 mm Hg $P_{I_{CO_2}}$ for 5 days and in six of seven subjects exposed to 30 mm Hg $P_{I_{CO_2}}$ environment for the same period. These occurred in the first 24 hr of exposure and disappeared by the second day in CO_2. The headaches were of a throbbing nature and were aggravated by the recumbent position and the

[2] Maximum work performance was judged by total exhaustion and in all cases was associated with plateauing of the heart rate greater than 190 beats/min.

TABLE 3. *Ventilation volumes*

Subj	$P_{I_{CO_2}}$, mm Hg	$\dot{V}_E$, liters/min BTPS			V_T, liters BTPS			Respiratory Rate		
		Rest	½	⅔	Rest	½	⅔	Rest	½	⅔
130	0	14.3	64.0	78.8	0.84	2.13	2.63	17	30	30
131		9.4	58.5	73.0	0.45	1.77	1.74	21	33	42
132		12.1	69.1	80.0	0.86	1.77	2.05	14	39	39
133		10.5	59.7	86.2	0.75	2.49	2.39	14	24	36
134		9.1	47.6	65.2	0.51	1.98	2.10	18	24	31
135		7.0	43.5	70.4	0.54	2.07	2.93	13	21	24
136		7.0		75.0	0.37		2.21	19		34
$\bar{X}$		9.9	57.1	75.5	0.62	2.04	2.29	16.6	28.5	33.7
SD		±2.7	±9.8	±6.9	±0.20	±0.27	±0.40	±3.0	±6.8	±6.0
130	8	11.0	59.7	89.6	0.58	1.99	2.72	19	30	33
131		12.7		70.3	0.64		2.13	20		33
132		10.0	57.1	79.0	0.59	1.37	2.19	17	33	36
133		11.2	60.6	83.8	0.59	2.02	2.15	19	30	39
134		13.6	62.3	75.5	0.80	1.60	1.94	17	39	39
135		10.0	55.4	62.3	0.71	2.05	2.60	14	27	24
136		11.2		90.0	0.56		1.88	20		48
$\bar{X}$		11.4	59.0*	78.6	0.64	1.81*	2.23	18.0	31.8*	36.0
SD		±1.3	±2.8	±10.2	±0.90	±0.30	±0.32	±2.2	±4.5	±7.3
130	15	15.5	73.5	87.6	0.74	2.72	2.65	21	27	33
131		17.1	66.9	84.5	1.01	2.03	2.22	17	33	38
132		13.9	60.3	84.3	0.77	1.55	2.48	18	39	34
133		11.8	78.0	73.9	0.69	1.86	2.11	17	42	35
134		11.6	74.5	70.5	0.64	2.07	1.81	18	36	39
135		10.7	51.4	67.8	0.82	2.14	2.61	13	24	26
136		15.1		95.8	0.76		2.13	20		45
$\bar{X}$		13.7	67.4	80.6	0.78	2.06	2.29	17.7	33.5	35.7
SD		±2.4	±10.1	±10.2	±0.12	±0.39	±0.31	±2.6	±6.9	±5.9
130	21	12.4	84.6	99.1	0.59	2.56	3.00	21	33	33
131		15.5	78.0	75.3	0.78	2.60	2.28	20	30	33
132		12.5	72.7	85.1	0.69	2.20	2.03	18	33	42
133		12.5	85.7	92.6	0.78	2.38	2.57	16	36	36
134		12.5	67.0	92.2	1.25	2.23	2.36	10	30	39
135		14.0	46.0	83.1	1.08	1.92	3.61	13	24	23
136		10.0		80.7	0.48		1.79	21		45
$\bar{X}$		12.8	72.3	86.9	0.81	2.32	2.52	17.0	31.0	35.9
SD		±1.7	±14.7	±8.2	±0.27	±0.25	±0.62	±4.2	±4.1	±7.2
130	30	21.5		90.5	0.90		2.51	24		36
131		24.1		85.5	1.42		2.38	17		36
132		24.5		107.2	1.11		2.75	22		39
133		23.4		109.5	1.30		2.81	18		39
134		25.0		100.8	1.39		2.40	18		42
135		24.3		104.3	1.62		3.48	15		30
136		26.4		126.1	1.06		2.47	25		51
$\bar{X}$		24.2		103.4	1.26		2.69	19.9		39.0
SD		±1.5		±13.3	±0.25		±0.39	±3.8		±6.5
P†		<.001	<.025	<.001	<.001	NS	<.025	NS	NS	NS
No. of subj		7	6	7	7	6	7	7	6	7

* These means are based on statistical estimates for *subject 131*.

† *P* values refer to significance of trend relating to $P_{I_{CO_2}}$ by analysis of variance.

Valsalva maneuver. They may have been caused by cerebral vascular dilation which occurs during exposure to increased $P_{I_{CO_2}}$ (23). In the present study, the added factor of exercise and sudden, rather than gradual, exposure to CO_2 may have modified the headache pattern. The headaches occurred at the 30 mm Hg $P_{I_{CO_2}}$ level only, but they did not appear or disappear in any pattern. In no case were they severe enough to interfere with the subjects' performance of exercise.

Premature ventricular contractions (PVC's) have not

TABLE 4. *Oxygen and carbon dioxide exchange*

Subj	$P_{I_{CO_2}}$, mm Hg	$\dot{V}_{O_2}$, liters/min STPD		$\dot{V}_{CO_2}$, liters/min STPD		Respiratory Exchange Ratio	
		½	⅔	½	⅔	½	⅔
130	0	1.965	2.516	1.723	2.707	.88	1.08
131		2.087	2.579	1.849	2.454	.89	.95
132		2.087	2.462	1.736	2.270	.83	.92
133		2.186	2.522	2.039	2.438	.93	.97
134		1.740	2.594	1.613	2.413	.93	.93
135		2.045	2.825	1.625	2.669	.79	.94
136			2.466		2.060		.84
$\bar{X}$		2.018	2.566	1.764	2.430	0.88	0.95
SD		±0.154	±0.125	±0.160	±0.223	±0.06	±0.07
130	8	1.835	2.871	1.574	2.402	.86	.84
131			2.517		2.164		.86
132		1.984	2.495	1.533	2.185	.77	.88
133		2.034	2.470	1.913	2.485	.94	1.00
134		1.934	2.377	1.647	2.335	.85	.98
135		2.049	2.151	1.931	2.155	.94	1.00
136			2.448		2.209		.90
$\bar{X}$		1.967*	2.476	1.720*	2.276	.87*	.92
SD		±0.087	±0.214	±0.189	±0.131	±0.07	±0.07
130	15	2.082	2.287	1.848	1.943	.89	.85
131		1.981	2.920	1.770	2.680	.89	.92
132		2.053	2.566	1.708	1.634	.83	.63
133		2.140	2.145	1.996	2.054	.93	.96
134		2.460	2.356	2.551	2.022	1.04	.86
135		1.920	2.410	1.803	2.121	.94	.88
136			2.242		1.933		.86
$\bar{X}$		2.106	2.418	1.946	2.057	.92	.85
SD		±0.190	±0.258	±0.312	±0.319	±0.07	±0.11
130	21	1.905	2.574	1.705	2.161	.90	.84
131		1.991	2.653	1.884	1.906	.95	.72
132		1.851	2.543	1.431	2.243	.77	.88
133		2.126	2.745	1.628	2.378	.77	.87
134		2.096	2.710	1.857	2.142	.89	.79
135		1.579	2.616	1.420	2.050	.90	.78
136			2.266		1.950		.86
$\bar{X}$		1.925	2.587	1.654	2.119	0.86	.82
SD		±0.200	±0.158	±0.201	±0.165	±0.08	±0.06
130	30		2.228		1.668		.75
131			2.486		1.785		.72
132			2.615		1.812		.69
133			2.423		1.827		.75
134			2.675		1.929		.72
135			2.839		2.068		.73
136			2.636		1.799		.68
$\bar{X}$			2.557		1.841		.72
SD			±0.198		±0.126		±0.03
P†		NS	NS	NS	<.001	NS	<.001

* These means are based on statistical estimates for *subject 131.*

† P values refer to significance of trend relating to $P_{I_{CO_2}}$ by analysis of variance.

been reported during hypercapnic studies in resting man with the $P_{I_{CO_2}}$ below 35 mm Hg (14, 27). Brackett et al. (5) observed no ECG changes in men exposed to 42 mm Hg $P_{I_{CO_2}}$. Other acute studies at $P_{I_{CO_2}}$ levels over 60 mm Hg have resulted in the occurrence of PVC's (24, 27). All these studies, however, involved man in a resting situation. Since one subject contributed to five of the nine incidents of ectopic foci and since the incidence of PVC's was not related solely to the hypercapnic environment, it is likely that these ectopic beats were exercise induced. PVC's are a frequent finding in normal men during exercise, and at the US Air Force School of Aerospace Medicine the incidence among apparently healthy pilots is over 30% (personal communication).

TABLE 5. *Mean rest-exercise blood gas changes*

Subj	$P_{I_{CO_2}}$	P_{O_2}, mm Hg		ΔP_{O_2}, mm Hg	P_{CO_2}, mm Hg		ΔP_{CO_2}, mm Hg	pH		ΔpH	Calculated HCO_3, mEq/liter		ΔHCO_3, mEq/liter
		Rest	Exer		Rest	Exer		Rest	Exer		Rest	Exer	
130	0	93.1	94.6	+1.5	38.5	35.4	−3.1	7.388	7.324	−.064	22.5	17.8	−4.7
131		88.4	84.8	−3.6	51.9	45.9	−6.0	7.398	7.344	−.054	31.0	24.2	−6.8
132		98.7	96.2	−2.5	37.5	37.4	−0.1	7.399	7.356	−.033	22.5	20.3	−2.2
133		108.8	94.3	−14.5	34.5	36.9	+2.4	7.385	7.310	−.075	20.0	18.0	−2.0
134		97.2	99.8	+2.6	36.8	37.8	+1.0	7.385	7.390	+.005	21.3	22.2	+1.9
135		86.4	95.9	+9.5	42.7	39.5	−3.2	7.373	7.341	−.032	24.1	20.7	−3.4
136		91.8	90.6	−1.2	38.3	39.6	+1.3	7.397	7.311	−.086	22.8	19.4	−3.4
$\bar{X}$		94.9	93.7	−1.2	40.0	38.9	−1.1	7.389	7.339	−.048	23.5	20.4	−2.9
SD		±7.5	±4.8	±7.3	±5.8	±3.4	±3.1	±.01	±.028	±.031	±3.6	±2.3	±2.7
P†			NS			NS			<.01				
130	8	108.7	110.4	+1.7	40.3	37.4	−2.9	7.378	7.270	−.106	23.0	16.6	−6.4
131		98.6	100.8	+2.2	40.2	39.5	−0.7	7.389	7.341	−.045	23.5	20.7	−2.8
132		105.6	104.2	−1.4	38.6	44.3	+5.7	7.401	7.319	−.082	23.2	22.1	−1.1
133		98.4	101.5	+3.1	42.7	43.7	+1.0	7.374	7.339	−.035	24.2	22.8	−1.4
134		103.1	98.0	−5.1	37.9	44.2	+6.3	7.371	7.320	−.051	21.3	22.1	+0.8
135		98.3	99.5	+1.2	42.3	39.7	−2.6	7.360	7.322	−.038	23.2	19.9	−3.3
136		103.1	114.7	+11.6	40.2	36.7	−3.5	7.392	7.359	−.033	23.7	20.1	−3.6
$\bar{X}$		102.3	104.2	+1.9	40.3	40.8	+.47	7.381	7.324	−.056	23.2	20.6	−2.5
SD		±4.0	±6.2	±5.1	±1.8	±3.3	±4.1	±.01	±.028	±.028	±0.9	±2.0	±2.3
P†			NS			NS			<.01				
130	15	116.7	118.9	+2.2	47.1	47.2	+0.1	7.347	7.326	−.021	25.0	23.9	−1.1
131		96.5	84.2	−12.3	41.3	52.0	+10.7	7.371	7.263	−.108	23.2	22.8	−0.4
132		102.9	99.4	−3.5	37.3	45.1	+7.8	7.348	7.277	−.071	19.9	20.4	+0.5
133		107.8	103.6	−4.2	46.3	49.4	+3.1	7.348	7.301	−.047	24.7	23.6	−1.1
134		109.7	104.2	−5.5	43.5	50.0	+6.5	7.367	7.316	−.051	24.2	24.7	+0.5
135		116.3	110.5	−5.8	46.7	50.2	+3.5	7.360	7.320	−.040	25.6	25.1	−0.5
136		116.7	101.9	−14.8	40.6	40.5	−0.1	7.406	7.318	−.088	24.7	20.1	−4.6
$\bar{X}$		109.5	103.2	−6.3	43.3	47.8	+4.5	7.364	7.303	−.061	23.9	22.9	−1.0
SD		±7.8	±10.6	±5.7	±3.7	±3.9	±4.0	±.02	±.024	±.030	±1.9	±2.0	±1.7
P†			.05 > P > .02			.05 > P > .02			<.01				
130	21	110.2	105.2	−5.0	42.8	48.6	+5.8	7.375	7.266	−.109	24.3	21.4	−2.9
131		105.4	95.6	−9.8	45.2	55.3	+10.1	7.382	7.278	−.104	26.0	25.1	−0.9
132		108.0	97.3	−10.7	41.2	51.1	+9.9	7.384	7.250	−.134	23.8	21.7	−2.1
133		113.1	103.0	−10.1	39.4	49.7	+10.3	7.367	7.308	−.059	21.9	24.2	+2.3
134		112.2	101.5	−10.7	41.9	53.8	+11.9	7.371	7.279	−.092	23.8	24.4	+0.6
135		111.3	102.6	−8.7	45.4	52.4	+7.0	7.367	7.286	−.081	25.6	24.4	−1.2
136		117.9	106.4	−11.5	44.3	49.3	+5.0	7.387	7.285	−.102	25.8	22.7	−3.1
$\bar{X}$*		111.2	101.7	−9.5	42.9	51.5	+8.6	7.376	7.279	−.097	24.4	23.4	−1.0
SD		±4.0	±3.9	±2.2	±2.2	±2.5	±2.6	±.01	±.01	±.028	±1.7	±1.6	±2.0
P†			<.01			<.01			<.01				
130	30	110.2	104.9	−5.3	46.4	57.2	+10.8	7.338	7.249	−.089	24.2	24.3	+0.1
131		106.6	95.6	−11.0	47.3	57.0	+9.7	7.364	7.291	−.073	26.1	26.6	+0.5
132		113.3	107.4	−5.9	45.2	54.3	+9.1	7.337	7.222	−.115	23.5	21.6	−1.9
133		118.2	104.4	−13.8	45.0	59.0	+14.0	7.353	7.262	−.091	24.2	25.8	+1.6
134		115.7	104.6	−11.1	47.3	61.6	+14.3	7.346	7.179	−.167	25.1	22.2	−2.9
135		120.8	104.9	−15.9	47.8	58.4	+10.6	7.359	7.249	−.100	26.1	24.8	−1.3
136		117.8	119.7	+1.9	42.9	48.7	+5.8	7.390	7.210	−.180	25.2	18.9	−6.3
$\bar{X}$		114.7	105.9	−8.7	46.0	56.6	+10.6	7.355	7.237	−.116	24.9	23.5	−1.5
SD		±5.0	±7.1	±6.1	±1.7	±4.1	±2.9	±.02	±.037	±.041	±1.0	±2.7	±2.6
P†			<.01			<.01			<.01				
P‡		<.001	<.01	<.01	<.025	<.001	<.001	<.001	<.001	<.005			

* Mean based on estimated values for *subject 134* and *subject 135*. † Significance of rest-exercise change (paired observation t test).
‡ Significance of variation with $P_{I_{CO_2}}$ (analysis of variance).

TABLE 6. *Maximum exercise runs*

Subj	$P_{I_{CO_2}}$, mm Hg	kg-m/min	$\dot{V}_E$	Resp Rate	Pulse Rate	Max $\dot{V}_{O_2}$	$\dot{V}_{CO_2}$	R	kcal/hr
130	0	2,233	143.9	48	192	3.627	3.604	.99	1,088
131		1,957	90.3	45	192	2.917	3.432	1.25	875
132		1,957	143.8	54	189	3.593	3.419	.95	1,078
133		1,866	144.8	51	198	3.374	3.811	1.13	1,012
134		2,141	147.5	51	180	3.567	4.241	1.19	1,070
135		2,416	163.0	51	201	4.395	4.688	1.07	1,319
136		2,019	152.5	65	195	3.486	3.755	1.08	1,046
137		1,866	110.9	33	195	3.358	3.775	1.12	1,007
$\bar{X}$		2,057	137.1	49.8	192.8	3.540	3.841	1.10	1,062
SD		±193	±24.0	±9.0	±6.4	±0.413	±0.430	±0.10	±124
130	8	2,141	159.3	48	192	3.422	3.675	1.07	1,027
131		2,141	117.5	36	195	4.103	4.368	1.06	1,231
132		2,141	140.0	51	189	3.330	3.632	1.09	999
133		1,866	134.2	48	204	3.503	3.738	1.07	1,051
134		1,866	136.8	48	173	3.680	3.928	1.07	1,104
135		2,233	152.6	48	204	4.266	4.139	.97	1,280
136		1,957	156.3	60	195	3.207	3.541	1.10	962
137		1,988	133.9	42	195	3.689	3.643	.99	1,107
$\bar{X}$		2,042	141.3	47.6	193.4	3.650	3.833	1.05	1,095
SD		±140	±14.0	±6.9	±9.8	±0.370	±0.289	±0.05	±111
130	21	2,049	169.1	48	192	3.436	3.308	.96	1,031
131		2,049	119.6	36	192	3.451	3.583	1.04	1,035
132		1,957	144.7	51	192	3.511	3.368	.96	1,053
133		2,049	146.8	45	195	3.440	3.380	.98	1,032
134		1,682	125.9	54	177	3.123	3.073	.98	937
135		2,141	156.0	48	192	3.807	3.589	.94	1,142
136		1,774	149.1	60	195	3.186	3.448	1.08	956
137		1,774	117.4	36	192	3.047	2.882	.95	914
$\bar{X}$		1,934	141.1	47.3	190.9	3.375	3.329	.99	1,013
SD		±168	±18.4	±8.3	5.8	±0.247	±0.244	±0.05	±74
*P**		NS	NS	NS	NS	NS	<.005	<.025	
No. of subj		8	8	8	8	8	8	8	

* *P* values refer to significance of trend relating to $P_{I_{CO_2}}$ by analysis of variance.

Ventilation Studies

Ventilation limitations may have altered the work capacity of the subjects and led to physiologic abnormalities. During maximum work runs when minute ventilation exceeded 130 liters/min [≈70% of maximum voluntary ventilation (MVV)], the subjects experienced intercostal muscle pain and dyspnea only when the $P_{I_{CO_2}}$ was at 21 mm Hg. Although the same level of ventilation was reached in 0 and 8 mm Hg $P_{I_{CO_2}}$, respiratory distress did not occur and generalized fatigue was the determining factor in ending these runs. It appears that an increase in Pa_{CO_2} rather than the magnitude of ventilation was the major cause of the subjective feeling of respiratory embarrassment. This was suggested by the observation that exercise at ⅔ maximum $\dot{V}_{O_2}$ in 30 mm Hg $P_{I_{CO_2}}$ was accompanied by complaints of dyspnea on two occasions even though $\dot{V}_E$ was only 50% of MVV. Dripps et al. (9) reported the observation that several of his subjects having $\dot{V}_E$ greater than 100 liters/min while breathing ambient air insisted that they had no dyspnea.

The significant increase in $\dot{V}_E$ during exercise with hypercapnia was not surprising and has been reported by others (1–3, 8, 13, 16). $\dot{V}_E$'s 10 times resting ambient levels were successfully maintained for the entire 30-min exercise period at the ⅔ workload in 30 mm Hg $P_{I_{CO_2}}$. While this $\dot{V}_E$ is only 50% of the subjects' MVV, it should be remembered that the MVV test usually is performed only over a 20-sec period. Freedman (12) has stated that after 4 min of hyperventilation, the maximum $\dot{V}_E$ is only 61% of the 15-sec MVV. In a recent study on MVV during exercise, Shephard (29) reported that while working at 80% of aerobic work capacity and simultaneously undergoing hypercapnic hyperventilation of 2% CO_2, men could attain only 80, 74, and 75% of MVV in the 5th, 10th, and 15th min of exercise, respectively. In addition, the mechanics of breathing while exercising on a bicycle have been found to be altered from the normal situation, even if the exercise is carried out in an ambient air environment (16). Dripps (9) reported that his subjects could reach only 66% of their MVV while performing strenuous muscular exercise on a stationary bicycle. How these findings are affected by the added stress of hypercapnia is not known, but it appears that some limitation to further V_T increases to achieve adequate ventilation was present in our subjects during the

TABLE 7. *Submaximum and maximum $\dot{V}_E$ comparison during maximum exercise testing*

Subj	½ Max $\dot{V}_{O_2}$		Max $\dot{V}_{O_2}$	
	0	21	0	21
130	51.1	89.4	143.9	169.1
131	23.4	60.4	90.3	119.6
132	54.0*	83.0	143.8	144.7
133	57.4	62.0*	144.8	146.8
134	47.4	58.2	147.5	125.9
135	46.6	50.5	163.0	156.0
136	58.9	72.3	152.5	149.1
137	35.9	56.4	110.9	117.4
$\bar{X}$	46.8	66.5	137.1	141.1
SD	±11.9	±13.7	±24.0	±18.4
P	<.01		NS	

* Estimated values from subjects' $\dot{V}_E$/watt load curve.

⅔ exercise level in 30 mm Hg $P_{I_{CO_2}}$ and maximum exercise in 21 mm Hg $P_{I_{CO_2}}$. This limitation may have contributed to the decreases in $\dot{V}_{CO_2}$ observed.

CO_2 Exchange

The observed fall in CO_2 respiratory exchange ($\dot{V}_{CO_2}$) with progressive increase in inspired CO_2 levels suggests a retention of CO_2 resulting in the buildup of body stores. Since the respiratory system is the primary route for CO_2 excretion, a buildup in stores may represent a failure of fully adequate ventilation. A decrease in $\dot{V}_{CO_2}$ in the face of a constant $\dot{V}_{O_2}$ and rising $P_{a_{CO_2}}$ does not suggest the possibility of a drop in CO_2 production by the tissues but points to a reduction in the amount which leaves the body. The explanation of why a higher level of ventilation at ⅔ maximum $\dot{V}_{O_2}$ (100 liters/min) in 30 mm Hg $P_{I_{CO_2}}$ would be inadequate to prevent CO_2 retention while a lower ventilation (75 liters/min) in ambient air would be fully adequate, may be found if the alveolar-inspired gradient for CO_2 is examined. In the ambient atmosphere which contains .03% CO_2, the lungs operate under a 38–42 mm Hg P_{CO_2} alveolar-inspired gradient. $P_{A_{CO_2}}$ is dependent on CO_2 production, alveolar ventilation ($\dot{V}_A$), and $P_{I_{CO_2}}$, and is described by the equation (22):

$$P_{A_{CO_2}} = \frac{.863\ \dot{V}_{CO_2}}{\dot{V}_A} + P_{I_{CO_2}} \qquad (1)$$

Thus, under normal ambient conditions such as alveolar ventilation of 5.5 liters/min and a $P_{A_{CO_2}}$ of 40 mm Hg, 250 ml of CO_2 will be excreted by the lungs each minute. The importance of the alveolar-inspired CO_2 gradient is shown by a rearrangement of *equation 1* (19):

$$(P_{A_{CO_2}} - P_{I_{CO_2}})\dot{V}_E = \dot{V}_{CO_2}\ (V_T/V_A)\ .863 \qquad (2)$$

Assuming a constant for the tidal volume/alveolar volume ratio (V_T/V_A),[3] the relationship between the gradient and $\dot{V}_E$ for a constant $\dot{V}_{CO_2}$ will be inversely proportional. At the 30 mm Hg $P_{I_{CO_2}}$ level, the normal alveolar-inspired gradient of 38 mm Hg in air was reduced to 16 mm Hg with a $\dot{V}_E$ of 24.2 liters/min at rest, and 26 mm Hg with a $\dot{V}_E$ of 103.4 liters/min during exercise. In the latter case, the ventilatory response and resultant decrease in alveolar-inspired gradient were such that a liter of alveolar ventilation was less effective in removing CO_2, thereby causing $P_{a_{CO_2}}$ and body stores to increase. Decreased efficiency of alveolar ventilation with CO_2 retention can be expected to continue until the mean pulmonary capillary P_{CO_2} and/or $\dot{V}_E$ increase sufficiently to restore equality between CO_2 production and CO_2 elimination.

Bullard (6) asserted that during heavy exercise with a $\dot{V}_{CO_2}$ of 3.5 liters/min a $\dot{V}_E$ of 88 liters/min was sufficient to keep $P_{a_{CO_2}}$ at 40 mm Hg in normocapnic atmospheres. Disproportionately higher ventilations would be needed to prevent $P_{a_{CO_2}}$ and CO_2 stores from rising in hypercapnic atmospheres. By calculation using *equation 2*, the subjects exercising in 30 mm Hg $P_{I_{CO_2}}$ would have had to raise their $\dot{V}_E$ to 113 liters/min to prevent the decrease in $\dot{V}_{CO_2}$ observed.[4] The reason why our subjects did not increase their ventilation is unclear but, since they had not yet reached a maximal mechanical limitation, CO_2 retention apparently was not an adequate stimulus to produce the additional increment of ventilation.

Acid-Base Changes

The rise in $P_{a_{CO_2}}$ from rest to exercise seen in this study is not the usual finding in the literature. While small increases of 2.5–5.0 mm Hg during light exercise have been described (4, 17, 30), the majority of studies have found no change (1, 18) in moderate exercise or a decrease in $P_{a_{CO_2}}$ (1, 10, 18, 31) in heavy exercise. Normocapnia during exercise has been used as evidence of respiratory competence even when maximum $\dot{V}_{O_2}$ has occurred and the cardiovascular system has reached its limit. The above studies, however, were at ambient conditions. Hickam's data (17) on untrained men in 5% CO_2 (≈36 mm Hg $P_{I_{CO_2}}$) show a rise in $P_{a_{CO_2}}$ of 12.8 mm Hg between rest and exercise as opposed to a 4.5 mm Hg rise in 0% CO_2. In this study at ⅔ maximum $\dot{V}_{O_2}$ in the 30 mm Hg $P_{I_{CO_2}}$ atmosphere, we found that a 10.6 mm Hg rise in $P_{a_{CO_2}}$ occurred in spite of a $\dot{V}_E$ increase to 103 liters/min. This was in contrast to a decrease of 1.1 mm Hg $P_{a_{CO_2}}$ associated with a $\dot{V}_E$ of 75.5 liters/min for the same exercise performance in air. The ensuing respiratory acidosis due to elevation of $P_{a_{CO_2}}$ should have accounted for a drop of .08 pH units instead of the .118 units decrease observed (21). This added pH drop and associated fall in bicarbonate was due to the metabolic acidosis which accompanies heavy exercise (1).

$\dot{V}_{O_2}$

The findings of no change in $\dot{V}_{O_2}$ with increasing $P_{I_{CO_2}}$ indicates that the metabolic cost of work is not influenced by hypercapnia. These results agree with Krasnogor's study in 8 mm Hg (20). Craig (8), however, found $\dot{V}_{O_2}$ to increase with increasing $P_{I_{CO_2}}$ in one subject doing submaximal work.

[3] It has been found that V_T/V_A will slightly decrease during exercise (1) and hypercapnic hyperventilation (26) since the rise in dead space is always proportionally smaller than the rise in tidal volume (V_T).

[4] This calculation was made using Kao's formula (19) assuming a constant 26 mm Hg P_{CO_2} gradient and a value of 1.14 for the V_T/V_A ratio based on data by Asmussen (1).

Conversely, a recent study by Finkelstein et al. (11) of maximum exercise at 0 and 16 mm Hg $P_{I_{CO_2}}$ showed a significant decrease in maximum $\dot{V}_{O_2}$ at the latter $P_{I_{CO_2}}$ level.

The US Air Force School of Aerospace Medicine Biometrics Division carried out analysis of variance on the data presented. The authors are deeply indebted to the personnel of the Environmental Systems Division of the US Air Force School of Aerospace Medicine and the participating subjects for their dedicated support of this study.

The research reported in this paper was conducted by personnel of the Sealed Environment Branch, Environmental Systems Division, US Air Force School of Aerospace Medicine, Aerospace Medical Division, AFSC, US Air Force, Brooks Air Force Base, Texas. This study was partially supported by National Aeronautics and Space Administration Defense PR T-63615(G). The voluntary informed consent of the subjects used in this research was obtained as required by AFR 169-8. Further reproduction is authorized to satisfy the needs of the US Government.

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Received for publication 7 November 1969.

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